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Barry S. Fogel

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

BE IT KNOWN, that I, Barry S. Fogel have invented certain new and useful improvements in
METHOD FOR TREATING PAINFUL CONDITIONS OF THE ANAL REGION AND
COMPOSITIONS THEREFOR of which the following is a specification:

Method for Treating Painful Conditions of the Anal Region and Compositions Therefor

Background of the Invention

This invention relates to methods and compositions for treating painful conditions of the anal region and more particularly for treating anal fissures, thrombosed or inflamed hemorrhoids, for pain associated with ligation of internal hemorrhoids and for chronic anal pain.

Anal fissures can be an extremely painful condition. The primary reason for severe pain is spasm of the anal sphincter. This spasm causes ischemia, which both produces pain and interferes with healing (Sharp, American Journal of Surgery, 1996; Volume 171, pages 512-515; Schouten et al., 1993, Scandinavian Journal of Gastroenterology, Volume 31, Supplement 218, pp. 78-81). Spasm of the anal sphincter also plays a role in the pain of inflammatory conditions of the anal region, such as inflamed or recently thrombosed hemorrhoids (Janicke & Pundt, 1996, Emergency Medicine Clinics of North America, Volume 14, pp. 757-788). See also, Madoff, RD., "Pharmacologic Therapy for Anal Fissure," New England Journal of Medicine 1998 Jan 22:338(4) 217-20.

Effective treatments for anal fissures, whether medical or surgical, involve relaxation of the spastic muscle. These treatments include lateral sphincterotomy, injection of the sphincter with botulinum toxin, and application of nitroglycerin ointment. A recent review by Sharp of treatment for chronic anal fissures recommends beginning with nitroglycerin ointment. If the fissure has not healed in six weeks, botulinum toxin injections are given. That review notes that "considerable educational effort is required to successfully adjust the dose" of nitroglycerin (Sharp, 1996, *ibid.*). It states that nitroglycerin "will often eliminate the severe pain of fissure-in-ano in 1 day". Schouten et al. (1993, *ibid.*) used topical isosorbide dinitrate to treat chronic anal fissures, attaining pain relief within 10 days". Lund & Scholefield (1997, *Lancet*, Volume 349, pp. 11-14) reported a randomized controlled trial of 0.2% nitroglycerin ointment for anal fissure. At 2 weeks, pain on defecation, as measured by a visual analogue scale (0=no pain,

- (X) the specification filed herewith
() U.S. Patent Application Serial Number _____
filed _____
() U.S. Patent Number _____
issued _____

If the rights of the above-identified small business concern are not exclusive, each individual, concern, or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor(s), who could not qualify as a small business concern under 37 CFR 1.9(d) or a non-profit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention, averring to their status as small entities. (37 CFR 1.27).

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I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))


I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Barry Fogel

TITLE OF PERSON: Managing Director, Synchronon LLC

ADDRESS OF PERSON: 48 Harwich Road, Providence, Rhode Island 02906

SIGNATURE



DATE

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has not been reported as a treatment for anal fissures. Sucralfate, when applied to a damaged mucosa, forms an adherent film that protects the mucosa and promotes healing (Kochhar et al., 1990; Diseases of the Colon and Rectum, Volume 33, pp. 49-51). In addition, sucralfate lowers local levels of the inflammatory mediator PGE₂ (Zahavi et al., 1989; Diseases of Colon and Rectum, Volume 32, pp. 95-98).

Summary of the Invention

One aspect of the invention is a composition comprising a combination of nitroglycerin and sucralfate. Yet another aspect is a composition comprising a combination of nitroglycerin, lidocaine and sucralfate. These compositions may be combined in a petrolatum base along with a water soluble lubricant such as K-Y™ Jelly. These compositions have analgesic properties.

Another aspect of the invention is a method for treating a painful condition on a body portion which includes providing a composition of nitroglycerin and sucralfate and applying the composition to the body. The composition may also include lidocaine. The compositions may further be mixed with an ointment base such as petrolatum and a water soluble lubricant. These ointments are particularly effective in treating painful conditions of the anal region by applying the composition to the anal region. Painful conditions which respond to the treatment of the invention include anal fissures, thrombosed or inflamed hemorrhoids, pain resulting from ligation of internal hemorrhoids and other chronic anal pain. A suitable water soluble lubricant is K-Y™ Jelly.

Description of the Preferred Embodiment

As discussed above, nitroglycerin alone and lidocaine alone have been proposed as a treatment for painful conditions in the anal area. The local anesthetic effect of lidocaine is based on a different mechanism of action than the analgesic effect of nitroglycerin. For this reason, I thought these two compounds might have additive or synergistic actions in the treatment of pain of anal fissures and other painful conditions in the anal region. I further reasoned that sucralfate might keep the other two ingredients adherent to the fissure, prolonging their action. Furthermore, the adherent film produced

by sucralfate might protect the raw area from irritation by the fecal stream. With these considerations in mind, I prepared a composition which was the combination of nitroglycerin and sucralfate. This formula was 60 grams of K-Y™ Jelly, 15 grams of 2% nitroglycerin ointment, and 6 grams of sucralfate. I prepared a second composition of
5 nitroglycerin, lidocaine and sucralfate in a base of petrolatum and a water soluble lubricant. The formulation was 240 grams petrolatum, 180 grams of K-Y™ Jelly, 60 grams of 2% nitroglycerin ointment, 30 grams of sucralfate and 9.6 grams lidocaine base. The amount of nitroglycerin may be in the range of 30-60 grams. The sucralfate was in powder form.

10 **Case 1:** A 49 year old man had a chronic anal fissure, which had persisted for several months, producing chronic rectal pain relieved only by narcotic analgesics. Anoscopy, performed separately by a rectal surgeon and a gastroenterologist, confirmed the presence of a moderately large anal fissure. The surgeon thought that surgery was necessary, and the gastroenterologist proposed cauterization. Neither felt that the fissure
15 would heal without invasive treatment of some kind.

The patient was first treated with nitroglycerin cream, 0.5%. (The cream was prepared by diluting 2% nitroglycerin ointment with a K-Y™ Jelly. This gave substantial but not complete pain relief that lasted about 2 hours, after which the pain gradually returned. Over several weeks, pain was relieved every time the cream was
20 applied, but returned if it was stopped. He was then switched to the combination of nitroglycerin and sucralfate. With this combination, relief lasted 3-4 hours at first, and then lasted longer and longer with repeated applications. Within two weeks, he had full relief applying the cream only twice a day. Within six weeks, the symptoms were totally relieved and the analgesic cream was no longer necessary.

25 **Subsequent Cases:** 4 subsequent patients, all but one with anoscopically confirmed anal fissures, were treated with the combination of nitroglycerin, lidocaine, and sucralfate, with the expectation of even better relief. (Patient #4 suffered from chronic anal pain of unknown cause.) All 4 of those treated obtained relief, and all chose to continue the medication for several days. Patients were instructed to use the cream as

often as they needed for pain relief they found satisfactory. The following table summarizes these patients' reports of their experience with the analgesic cream:

	Patient: Sex and age	1: ♀ 47	2: ♀ 37	3: ♂ 69	4: ♂ 54 (chronic anal pain)
	Duration of pain before treatment	1 week	2 weeks	5 weeks	2 years of discomfort, 5 months of pain
5	Other treatment tried	None	Generic hemorrhoid cream	Anusol™, Nupercainal™, sitz baths	None
	Time from application to relief	30 minutes	5 minutes	30 minutes	5-10 minutes
	Percentage of pain remaining after application of the cream	25%	50%	50%	No pain
	Times a day applied	2	2-3	2	2
10	Persistence of benefit	Yes	Yes	Yes	Yes
	Resolution of painful condition	Yes	Yes	Yes	Partial
	Time to resolution of condition	2 weeks	1 week	1 week	Severe pain resolved in 1 week
	Side effects	Headache	Headache, burning sensation	None	Burning sensation
15	Stopped medication because of side effects	No	No	No	No
	Persistence of side effects	No	Yes	N/A	No

Five patients, all with anoscopically confirmed fissures, received jars of the analgesic cream, and were instructed to apply it as needed to eliminate their pain. All got complete relief within minutes. The complete relief they obtained contrasted with the partial relief usually reported by patients treated with nitroglycerin ointment alone. Applications about four times daily were adequate to completely control their pain. Three of the patients had been scheduled for surgery to treat their fissures. They had been given the cream 3 to 4 weeks before the date planned for the operation. All three patients cancelled their operations, because they had had sufficient pain relief. One underwent repeat anoscopy, which revealed complete healing of the fissure.

None of the 5 patients required any oral analgesics, sitz baths, or other treatments to relieve pain, as soon as they had access to the nitroglycerin-lidocaine-sucralfate cream.

An additional experiment was performed to establish the effect of the sucralfate. A 64 year old man with severe pain following the rubber band ligation of a hemorrhoid was treated. He had had six weeks of pain prior to the treatment. We treated him on

alternate days with either the composition including nitroglycerin, lidocaine and sucralfate or the composition without the sucralfate. He was instructed to reapply the formula any time the pain began to recur. The three ingredient formula gave 90% relief (i.e., pain reduced to 10% of baseline) within fifteen minutes. The patient applied the cream three more times during the next twenty-four hours obtaining satisfactory relief.

The formulation without sucralfate gave less relief, and the pain recurred sooner. The patient applied the two-ingredient (without sucralfate) formula a total of five more times during the next twenty-four hours. Not only did the three-ingredient (with sucralfate) formula act faster, but it was associated with a less severe headache than the two-ingredient formula. The two-ingredient formula may have caused a worse headache because the patient might have used more of it to get relief. Alternatively, the sucralfate in the three-ingredient formula may have slowed the systemic absorption of nitroglycerin.

An additional three patients were treated with various formulations to establish the benefit of sucralfate and to illustrate that the concentration of nitroglycerin needed to treat anal fissure can be lower than that reported in the literature. These cases also show that adding nitroglycerin to the sucralfate-lidocaine combination improves efficacy. The three additional cases are shown in the table below:

Patient: Sex and age	1: ♀ 68	2: ♂ 81	3: ♂ 33
Diagnosis	Anal fissure	Anal fissure	Inflamed hemorrhoid
Duration of pain before treatment	6 months	3 months	2 months
Other treatment tried	None	Sitz baths, suppositories; cortisone cream	Desitin ointment
Time from application to relief	30 minutes	15 minutes	5 minutes
Percentage of pain remaining after application of the cream	25%	70% after first application; almost none after 4 weeks	Complete relief
Times a day applied	5	2-3	3-4
Persistence of benefit	Yes	Yes	Yes
Resolution of painful condition	Yes	Yes	Yes, but it recurs occasionally
Time to resolution of condition	Not known	4 weeks	Not known
Side effects	None	None	No
Stopped medication because of side effects	No	No	No
Persistence of side effects	N/A	N/A	N/A

Patient #1 received the nitroglycerin-lidocaine-sucralfate formula discussed above (formula A) and a formulation without sucralfate (formula B) in the sequence A-B-A over three days. The reported benefit shown in the table above resulted from use of formula A. Formula B was not tolerated; it produced a throbbing headache. This case suggests that sucralfate may actually provide some protection against nitroglycerin-induced headache, perhaps by influencing the absorption of the nitroglycerin.

Patient #2 in the table above received a modified formula with 30 grams of 2% nitroglycerin ointment per 500 grams of the nitroglycerin-lidocaine-sucralfate mixture. The concentration of nitroglycerin in this mixture -- 0.12% -- was lower than the 0.2% concentration reported in recent randomized controlled trials of the use of nitroglycerin as a single agent. Nonetheless, the mixture was efficacious and did not cause headaches (or any other side effects). This case supports the inventor's premise that nitroglycerin in combination with sucralfate and lidocaine is superior to nitroglycerin alone. The combination is efficacious at lower doses of nitroglycerin and the combination is less likely to cause headache.

Patient #3 received formula A and a formulation without nitroglycerin (formula C) in the sequence A-C-A over three days. This formula C (without nitroglycerin) did not give complete relief; the patient estimated that 25% of the pain remained after application. This case supports the relevance of nitroglycerin to the analgesic activity of the mixture, even in conditions other than anal fissure, where the efficacy of nitroglycerin is well established.

Conclusions: A topical analgesic cream or ointment for anal fissures that contains nitroglycerin will be more efficacious if it also contains sucralfate. A cream or ointment containing nitroglycerin, sucralfate, and lidocaine is especially efficacious.

Other anal and rectal conditions, such as inflamed hemorrhoids, produce pain for the same reasons as an anal fissure -- a combination of inflammation and spasm of the anal sphincter. Therefore, the combination cream or ointment is expected to be similarly helpful for the pain of those conditions (as demonstrated in patient #3 in the table above). The cream or ointment may also provide relief for pain following rubber band ligation of internal hemorrhoids, as this procedure often leads to sphincter spasm and local

inflammation. Finally, the fourth additional case shows that the cream or ointment may be helpful for chronic anal pain of unknown cause.

The triple combination is more likely to produce complete and rapid pain relief than either nitroglycerin or lidocaine alone. It may provide a longer duration of relief than nitroglycerin, as well. Despite the availability of all of the ingredients for many years, there are no reports of the combination being tested as a treatment for the pain of anal fissures or related conditions.

What is claimed is:

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1. Composition comprising a combination of nitroglycerin and sucralfate.
2. Composition comprising a combination of nitroglycerin, lidocaine and sucralfate.
3. The composition of claims 1 or 2 wherein the combination is in a petrolatum base.
4. The composition of claim 3 further including a water soluble lubricant.
5. Analgesic composition comprising:
nitroglycerin and sucralfate in an ointment or cream base.
6. Analgesic composition comprising:
nitroglycerin, lidocaine and sucralfate in an ointment or cream base.
7. The analgesic composition of claims 5 or 6 wherein the ointment or cream base comprises petrolatum and a water soluble lubricant.
8. Method for treating a painful condition on a body comprising:
providing a composition of nitroglycerin and sucralfate; and
applying the composition to the body.
9. Method for treating a painful condition on a body comprising:
providing a composition of nitroglycerin, lidocaine and sucralfate; and
applying the composition to the body.
10. Method of claims 8 or 9 wherein the providing further includes mixing the composition in an ointment or cream base.
11. Method of claim 10 wherein the ointment or cream base comprises petrolatum and a water soluble lubricant.
12. Method for treating painful conditions of the anal region comprising:
providing a composition of nitroglycerin and sucralfate; and
applying the composition to the anal region.
13. Method for treating painful conditions of the anal region comprising:
providing a composition of nitroglycerin, lidocaine and sucralfate; and
applying the composition to the anal region.
14. The method of claims 12 or 13 wherein the composition includes an ointment or cream base.

15. The method of claim 14 wherein the ointment or cream base comprises petrolatum and a water soluble lubricant.

16. The method of claims 12 or 13 wherein the painful condition is an anal fissure.

5 17. The method of claims 12 or 13 wherein the painful condition is thrombosed or inflamed hemorrhoids.

18. The method of claims 12 or 13 wherein the painful condition results from ligation of internal hemorrhoids.

10 19. Method for treating a painful condition of the anal region comprising:
providing a composition of nitroglycerin, lidocaine and sucralfate in a base of petrolatum and a water soluble lubricant; and
applying the composition to the anal region.

20. The method of claim 19 wherein the composition comprises approximately 240 grams petrolatum, 180 grams of lubricant, 60 grams 2% nitroglycerin,
15 30 grams sucralfate and 9.6 grams lidocaine.

21. The method of claim 20 wherein the lubricant is K-Y™ jelly.

1974 1975 1976 1977 1978 1979 1980 1981 1982 1983 1984 1985 1986 1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2039 2040 2041 2042 2043 2044 2045 2046 2047 2048 2049 2050 2051 2052 2053 2054 2055 2056 2057 2058 2059 2060 2061 2062 2063 2064 2065 2066 2067 2068 2069 2070 2071 2072 2073 2074 2075 2076 2077 2078 2079 2080 2081 2082 2083 2084 2085 2086 2087 2088 2089 2090 2091 2092 2093 2094 2095 2096 2097 2098 2099 2100 2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2113 2114 2115 2116 2117 2118 2119 2120 2121 2122 2123 2124 2125 2126 2127 2128 2129 2130 2131 2132 2133 2134 2135 2136 2137 2138 2139 2140 2141 2142 2143 2144 2145 2146 2147 2148 2149 2150 2151 2152 2153 2154 2155 2156 2157 2158 2159 2160 2161 2162 2163 2164 2165 2166 2167 2168 2169 2170 2171 2172 2173 2174 2175 2176 2177 2178 2179 2180 2181 2182 2183 2184 2185 2186 2187 2188 2189 2190 2191 2192 2193 2194 2195 2196 2197 2198 2199 2200 2201 2202 2203 2204 2205 2206 2207 2208 2209 2210 2211 2212 2213 2214 2215 2216 2217 2218 2219 2220 2221 2222 2223 2224 2225 2226 2227 2228 2229 2230 2231 2232 2233 2234 2235 2236 2237 2238 2239 2240 2241 2242 2243 2244 2245 2246 2247 2248 2249 2250 2251 2252 2253 2254 2255 2256 2257 2258 2259 2260 2261 2262 2263 2264 2265 2266 2267 2268 2269 2270 2271 2272 2273 2274 2275 2276 2277 2278 2279 2280 2281 2282 2283 2284 2285 2286 2287 2288 2289 2290 2291 2292 2293 2294 2295 2296 2297 2298 2299 2300 2301 2302 2303 2304 2305 2306 2307 2308 2309 2310 2311 2312 2313 2314 2315 2316 2317 2318 2319 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329 2330 2331 2332 2333 2334 2335 2336 2337 2338 2339 2340 2341 2342 2343 2344 2345 2346 2347 2348 2349 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 2368 2369 2370 2371 2372 2373 2374 2375 2376 2377 2378 2379 2380 2381 2382 2383 2384 2385 2386 2387 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 2399 2400 2401 2402 2403 2404 2405 2406 2407 2408 2409 2410 2411 2412 2413 2414 2415 2416 2417 2418 2419 2420 2421 2422 2423 2424 2425 2426 2427 2428 2429 2430 2431 2432 2433 2434 2435 2436 2437 2438 2439 2440 2441 2442 2443 2444 2445 2446 2447 2448 2449 2450 2451 2452 2453 2454 2455 2456 2457 2458 2459 2460 2461 2462 2463 2464 2465 2466 2467 2468 2469 2470 2471 2472 2473 2474 2475 2476 2477 2478 2479 2480 2481 2482 2483 2484 2485 2486 2487 2488 2489 2490 2491 2492 2493 2494 2495 2496 2497 2498 2499 2500 2501 2502 2503 2504 2505 2506 2507 2508 2509 2510 2511 2512 2513 2514 2515 2516 2517 2518 2519 2520 2521 2522 2523 2524 2525 2526 2527 2528 2529 2530 2531 2532 2533 2534 2535 2536 2537 2538 2539 2540 2541 2542 2543 2544 2545 2546 2547 2548 2549 2550 2551 2552 2553 2554 2555 2556 2557 2558 2559 2560 2561 2562 2563 2564 2565 2566 2567 2568 2569 2570 2571 2572 2573 2574 2575 2576 2577 2578 2579 2580 2581 2582 2583 2584 2585 2586 2587 2588 2589 2590 2591 2592 2593 2594 2595 2596 2597 2598 2599 2600 2601 2602 2603 2604 2605 2606 2607 2608 2609 2610 2611 2612 2613 2614 2615 2616 2617 2618 2619 2620 2621 2622 2623 2624 2625 2626 2627 2628 2629 2630 2631 2632 2633 2634 2635 2636 2637 2638 2639 2640 2641 2642 2643 2644 2645 2646 2647 2648 2649 2650 2651 2652 2653 2654 2655 2656 2657 2658 2659 2660 2661 2662 2663 2664 2665 2666 2667 2668 2669 2670 2671 2672 2673 2674 2675 2676 2677 2678 2679 2680 2681 2682 2683 2684 2685 2686 2687 2688 2689 2690 2691 2692 2693 2694 2695 2696 2697 2698 2699 2700 2701 2702 2703 2704 2705 2706 2707 2708 2709 2710 2711 2712 2713 2714 2715 2716 2717 2718 2719 2720 2721 2722 2723 2724 2725 2726 2727 2728 2729 2730 2731 2732 2733 2734 2735 2736 2737 2738 2739 2740 2741 2742 2743 2744 2745 2746 2747 2748 2749 2750 2751 2752 2753 2754 2755 2756 2757 2758 2759 2760 2761 2762 2763 2764 2765 2766 2767 2768 2769 2770 2771 2772 2773 2774 2775 2776 2777 2778 2779 2780 2781 2782 2783 2784 2785 2786 2787 2788 2789 2790 2791 2

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COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

METHOD FOR TREATING PAINFUL CONDITIONS OF THE ANAL REGION AND COMPOSITIONS THEREFOR

the specification of which (I authorize Choate, Hall & Stewart to check one of the following, three choices, and fill in the blanks, if applicable):

 X is attached hereto

 was filed on as Application
Serial No. and amended on (if
applicable).

 was filed as PCT international application No. ,
on and was amended under PCT Article 19
on (if applicable).

I hereby state that I have reviewed and understood the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledged the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):

Priority Claimed

<u> </u> (Number)	<u> </u> (Country)	<u> </u> (Day/Month/Year/Filed)	<u> </u> Yes	<u> </u> No
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<u> </u> (Number)	<u> </u> (Country)	<u> </u> (Day/Month/Year/Filed)	<u> </u> Yes	<u> </u> No
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THE UNIVERSITY OF CHICAGO

[illegible]

(PCT Appl. No.)	(U.S.S.N.)	(status-patented, pending, abandoned)
90/06780	08/000,000	patented
90/06781	08/000,000	patented
90/06782	08/000,000	patented
90/06783	08/000,000	patented
90/06784	08/000,000	patented
90/06785	08/000,000	patented
90/06786	08/000,000	patented
90/06787	08/000,000	patented
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90/06855	08/000,000	patented
90/06856	08/000,000	patented
90/06857	08/000,000	patented
90/06858	08/000,000	patented
90/06859	08/000,000	patented
90/06860	08/000,000	patented
90/06861	08/000,000	patented
90/06862	08/000,000	patented
90/06863	08/000,000	patented
90/06864	08/000,000	patented
90/06865	08/000,000	patented
90/06866	08/000,000	patented
90/06867	08/000,000	patented
90/06868	08/000,000	patented
90/06869	08/000,000	patented
90/06870	08/000,000	patented
90/06871	08/000,000	patented
90/06872	08/000,000	patented
90/06873	08/000,000	patented
90/06874	08/000,000	patented
90/06875	08/000,000	patented
90/06876	08/000,000	patented
90/06877	08/000,000	patented
90/06878	08/0	

Provisional Application(s):

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:
Sam Pasternack, Reg. No. 29,576; David J. Powsner, Reg. No. 31,868; Mary Rose Scozzafava, Reg. No. 36,268; Mary Raynor Jimenez, Reg. No. 37,219; Brenda Herschbach Jarrell, Reg. No. 39,223; Douglas D. Robinow, Reg. No. 40,787 and Kevin M. Tormey, Reg. No. 41,351.

Address all correspondence to Sam Pasternack, Choate, Hall & Stewart, Exchange Place, 53 State Street, Boston, Massachusetts 02109-2891.

1. The first step is to identify the problem. This involves understanding the current situation and what needs to be changed.

- (X) the specification filed herewith
() U.S. Patent Application Serial Number _____
filed _____
() U.S. Patent Number _____
issued _____

If the rights of the above-identified small business concern are not exclusive, each individual, concern, or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor(s), who could not qualify as a small business concern under 37 CFR 1.9(d) or a non-profit organization under 37 CFR 1.9(e).

*NOTE: Separate verified statements are required from each named person, concern, or organization having rights to the invention, averring to their status as small entities. (37 CFR 1.27).

FULL NAME: _____
ADDRESS: _____
(X) INDIVIDUAL () SMALL BUSINESS CONCERN () NON-PROFIT ORGANIZATION

FULL NAME: _____
ADDRESS: _____
(X) INDIVIDUAL () SMALL BUSINESS CONCERN () NON-PROFIT ORGANIZATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Barry Fogel

TITLE OF PERSON: Managing Director, Synchronon LLC

ADDRESS OF PERSON: 48 Harwich Road, Providence, Rhode Island 02906

SIGNATURE

Barry Fogel

DATE

2/25/98